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A Stereocontrolled Synthesis of (±)-Xenovenine via a Scandium(III)-Catalyzed Internal Aminodiene Bicyclization Terminated by a 2-(5-Ethyl-2-thienyl)ethenyl Group

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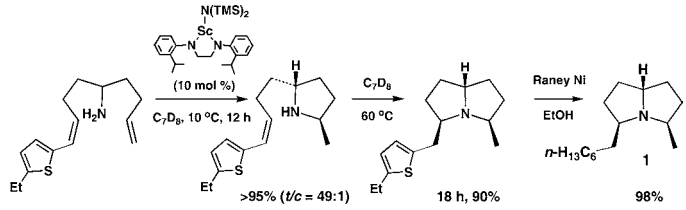
ABSTRACT



A highly diastereoselective binary hydroamination of a 5-amino-1,8-diene containing a 2-(5-ethyl-2-thienyl)ethenyl terminator has been utilized in an efficient synthesis of (±)-xenovenine (1). A pronounced rate enhancement was observed for cyclization onto the 2-(heteroaromatic)ethenyl group in comparison to a simple 1,2-disubstituted alkene.

The catalytic hydroamination of alkenes constitutes a synthetic route to amines that is endowed with exceptional atom economy. Although main-group metal complexes have been used as catalysts for alkene hydroamination,[1a] the most general cases for the synthesis of amines and their derivatives involve transition metal catalysis using complexes of rhodium,[1b−d] ruthenium,[1e,f] nickel[1g−i] and palladium,[1j−p] gold,[1q−s] as well as the group 3[2a−n] and group 4[2o−y] metals. In contrast to catalysis by complexes of the late transition metals, hydroaminations involving complexes of the group 3 metals proceed via syn-addition of the metal-amido (M−N) bond to the C=C double bond.[2a,b] In addition, diastereoselectivities associated with intramolecular hydroaminations of chiral substrates by group 3 metals are correlated with both the covalent radius of the metal and its ligand environment.[2a] We have previously shown that a nonmetallocene complex of Sc(III) supported by a strongly electron-donating chelating diamide ligand (e.g., **3**) provides superb trans/cis selectivities in the cyclization of 2-substituted-4-pentenamines.[2c] In this communication, we describe an efficient synthesis of (±)-xenovenine (**1**) that relies on rate enhancement attributable to an unprecedented Sc(III)-catalyzed internal hydroamination involving a 2-(5-ethyl-2-thienyl)ethenyl terminator, which serves as a surrogate for a conventional alkyl group.

The toxic pyrrolizidine alkaloid (+)-xenovenine (**1**) was isolated from the skin of the frog *Solenopsis xenoveneum* in 1980.[3] From a biological standpoint it is noteworthy that this defense alkaloid is not produced by the frog but instead originates in the venom of ants that constitute, in part, the diet of the amphibian. Xenovenine (**1**) has been the subject of six total syntheses,[4a−h] one of which involved a sequential bicyclization of an amino(allene)ene in the presence of a constrained Sm(III) metallocene catalyst, where initial cyclization occurred at the more reactive allene.[4c]

We have reported that 5-amino-1,8-nonadiene (**2a**) undergoes smooth sequential bicyclization to pyrrolizidine **5a**

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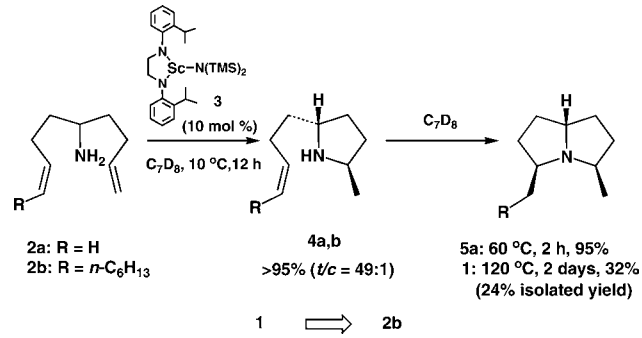
via pyrrolidine **4a** in the presence of complex **3** (5 mol %).[2c] The most direct and obvious route to (±)-xenovenine (**1**) should therefore entail an analogous bicyclization of aminodiene **2b**. Unfortunately, common 1,2-disubstituted alkenes are known to be very reluctant participants in internal hydroaminations catalyzed by group 3 complexes.[2d,e] This indeed proved to be the case as **2b**, although subject to facile monocyclization to provide **4b** (t/c = 49:1, characterized as the *p*-toluenesulfonamide), underwent the required subsequent cyclization only with great lethargy and incompletely at 120 °C (Scheme 1).

We have previously demonstrated that a representative primary amine bearing a 2-(phenyl)ethenyl moiety (e.g., 1-amino-2,2-dimethyl-5-phenyl-(*E*)-4-pentene) undergoes internal hydroamination at a significantly faster rate than simple 1,2-disubstituted aminoalkenes (i.e., 1-amino-2,2-dimethyl-(*E*)-4-hexene).[2d,h] In light of this, it seemed reasonable that terminal substitution by heteroaromatic groups might also lead to rate acceleration of internal hydroamination. To test this hypothesis in the context of the synthesis of (±)-xenovenine (**1**), the aminodiene **2c** was prepared according to the following protocol.

Scheme 1. Binary Hydroamination of Nonconjugated Aminodienes



Sequential lithiation of 5-hexen-2-one *N*,*N*-dimethylhydrazone **6** (LDA, THF) followed by alkylation with 1,3-dibromo-2-propene (THF, −78 → 0 °C) and subsequent hydrolysis (H_3O^+) furnished ketone **7b** as a mixture of *Z*- and *E*-isomers in 94% overall yield. Coupling of 5-ethylthiophene-2-boronic acid (**8**)[5] with **7b** [$Pd(PPh)_4$ (5 mol %), Na_2CO_3, LiCl, 1,2-DME] provided ketone **9** in 66% yield as a 4:1 mixture of *Z*- and *E*-geometrical isomers, from which the pure *Z*-isomer could be obtained in 48% isolated yield by chromatography on silica gel. Reductive amination of (*Z*)-**9** ($NaBH_3CN$, NH_4OAc, MeOH) then delivered the requisite aminodiene **2c** in 85% isolated yield. Exposure of **2c** to complex **3**[2c] (10 mol %, toluene-d_8, 10 °C) resulted in an efficient and highly diastereoselective monocyclization to generate 2,5-disubstituted pyrrolidine **4c** (t/c = 49:1, characterized as the *p*-toluenesulfonamide) with >95% conversion. It is significant that simply increasing the reaction temperature to 60 °C led to comparatively rapid (18 h) and stereospecific bicyclization to afford pyrrolizidine **5c** in 90% yield [(NMR), 86% after chromatography]. Reductive desulfurization of **5c** (Raney-Ni, EtOH, 23 °C) ultimately secured (±)-xenovenine (**1**)[6] in 98% yield (44% overall in five steps from hydrazone **6**) after purification by bulb-to-bulb distillation (Scheme 2).

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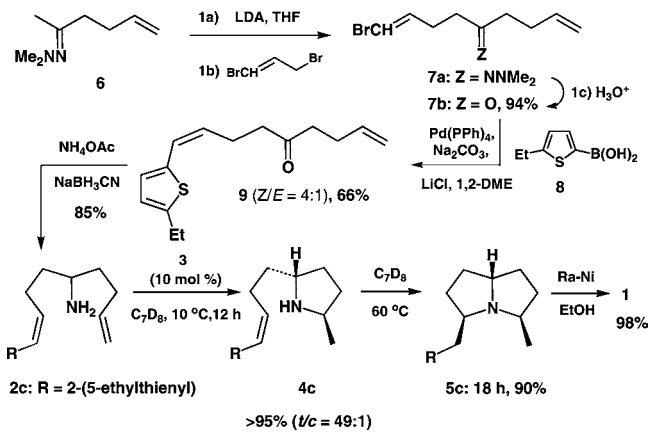
(5) Conveniently prepared in 72% overall yield by the sequential lithiation of 2-ethylthiophene (*n*-BuLi) followed by the addition of the resulting organolithium to $B(OMe)_3$ and hydrolysis.

(6) (±)-Xenovenine prepared in this manner was spectroscopically identical to the natural and previously synthesized products.

Scheme 2. Internal Hydroamination of a 2-(Heteroaryl)ethenyl Substituent



The foregoing application vividly illustrates a pronounced cyclization rate enhancement involving a 2-(heteroaromatic)ethenyl substituent as compared to the corresponding saturated 2-(alkyl)alkene in a Sc(III)-catalyzed hydroamination. As the latter have proven substantial obstacles to the general utilization of internal hydroaminations catalyzed by early metal complexes in synthesis, the novel strategy described here is expected to enable new pathways to target molecules of interest.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, **2b**, **2c**, **4b**$_{NTs}$, **4b**$_{NTs}$, **5c**, **6**, **7**, **9**, and their precursors. This material is available free of charge via the Internet at http://pubs.acs.org.

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